Journal of the American College of Cardiology
© 2001 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 37, No. 7, 2001
ISSN 0735-1097/01/$20.00
PII S0735-1097(01)01234-7

Plaque Distribution and Vascular Remodeling of Ruptured and Nonruptured Coronary Plaques in the Same Vessel: An Intravascular Ultrasound Study In Vivo

Clemens von Birgelen, MD, PHD,* Wolfgang Klinkhart, MD,* Gary S. Mintz, MD, FACC,† Alexandra Papatheodorou, MD,* Jörg Herrmann, MD,* Dietrich Baumgart, MD,* Michael Haude, MD,* Heinrich Wieneke, MD,* Junbo Ge, MD,* Raimund Erbel, MD, FACC*

Essen, Germany and Washington, D.C.

OBJECTIVES This study was designed to identify potential differences between the intravascular ultrasound (IVUS) characteristics of spontaneously ruptured and nonruptured coronary plaques.

BACKGROUND The identification of vulnerable plaques in vivo may allow targeted prevention of acute coronary events and more effective evaluation of novel therapeutic approaches.

METHODS Intravascular ultrasound was used to identify 29 ruptured plaques in arteries containing another nonruptured plaque in an adjacent segment. Intravascular ultrasound characteristics of these plaques were compared with plaques of computer-matched controls without evidence of plaque rupture. Plaque distribution was assessed by measuring the eccentricity of lumen location (inside the total vessel). Lumen cross-sectional area narrowing was calculated as [1 − (target/reference lumen area)] × 100%. A remodeling index was calculated as lesion/reference arterial area (>1.05 = compensatory enlargement, <0.95 = shrinkage).

RESULTS Among the three groups of plaques, there was no significant difference in quantitative angiographic parameters, IVUS reference dimensions and IVUS lumen cross-sectional area narrowing. There was a difference in plaque distribution; lumen location by IVUS was significantly more eccentric in ruptured than in nonruptured ($p = 0.002$) and control plaques ($p < 0.0001$). The arc of disease-free vessel wall was larger in ruptured than in control plaques ($p < 0.0001$). The remodeling pattern of ruptured and nonruptured plaques differed significantly from that of the control plaques ($p = 0.0001$ and 0.003); compensatory enlargement was found in 66%, 48%, and 17%, whereas shrinkage was found in 7%, 10% and 48%, respectively.

CONCLUSIONS Intravascular ultrasound assessment of plaque distribution and vascular remodeling may help to classify plaques with the highest probability of spontaneous rupture. (J Am Coll Cardiol 2001;37:1864–70) © 2001 by the American College of Cardiology

Spontaneous rupture of lipid-laden plaques is an important trigger of thrombus formation and acute coronary syndromes (1–3). Much of our knowledge of plaque rupture has been derived from histopathologic studies following fatal events. Postmortem data suggested that plaque rupture mainly occurs in severely atherosclerotic vessels (4–6), whereas angiographic studies suggested that plaque rupture occurs in insignificant, mildly occlusive plaques (7,8). One explanation of this contradiction is vascular remodeling (8,9), the increase in total arterial area that accompanies plaque accumulation (10–13). Angiography is unsuitable for an investigation of the amount of plaque rupture because of the remodeling process (10–20).

Intravascular ultrasound (IVUS) permits transmural visualization of coronary arteries and assessment of lumen narrowing and vessel remodeling by comparing lesion and reference segments (11,15–20). Intravascular ultrasound can also be useful in confirming the presence of plaque rupture (21–25). The aim of the present IVUS study was to evaluate possible intraindividual differences between ruptured and nonruptured plaques in the same artery and to compare these plaques with matched control plaques from our database.

From the *Department of Cardiology, University Essen, Essen, Germany, and the †Washington Hospital Center, Washington, D.C.

Manuscript received May 4, 2000; revised manuscript received January 30, 2001, accepted February 15, 2001.

METHODS

Study population. Between August 1, 1996, and March 1, 1999, we prospectively performed diagnostic IVUS before coronary interventions to identify spontaneous plaque rupture in previously untreated coronary arteries in 153 patients with unstable angina, who had previously received neither GP IIa/IIIa antagonists nor thrombolytic therapy. Of 51 patients with IVUS-documented plaque rupture, 29 had another focal nonruptured plaque in an adjacent segment of the same artery (Fig. 1); both plaques met the following IVUS criteria: 1) high-quality images of the lesion as well as the proximal and distal reference segments, 2) nonostial lesion location, 3) calcification that did not limit quantitative assessment of arterial area, 4) absence of side branches between the lesion and the proximal and distal reference segments and 5) absence of very angular segments on angiography.

The ruptured plaques were compared with the nonruptured plaques; 15 were proximal and 14 distal to the

Abbreviations and Acronyms

EEM	= external elastic membrane
EEM-D1	= EEM diameter at P–M-Tmax
IVUS	= intravascular ultrasound
P+M	= plaque plus media
P+M-Tmax	= maximal P+M thickness
P+M-Tmin	= minimal P+M thickness

ruptured plaques. The nonruptured plaques served as an "internal" control group, that is, plaques exposed to the same risk factors and genetic features.

The study was approved by the Local Council on Human Research, and all patients signed a written informed consent form approved by the Local Medical Ethics Committee.

Matched controls. We also compared the ruptured plaques with a matched group of plaques (control plaques) from patients who had no acute coronary syndromes or IVUS evidence of plaque rupture. To avoid a potential influence of differences in patients' gender, plaque location and degree of lumen narrowing, computer-assisted matching of plaques from our database of 530 de novo (i.e., no previous intervention) atherosclerotic plaques was performed. The IVUS assessment of the entire range of atherosclerotic disease is an important field of research in our institution; thus, this database includes many nontarget lesion plaques that frequently had an insignificant lumen narrowing. For matching purposes access to many data of nontarget lesion plaques was important, as many ruptured plaques had quite preserved lumen dimensions. Matching criteria included: 1) identical gender (no difference), 2) identical coronary artery segment, such as proximal LAD (no difference) and 3) similar degree of IVUS lumen area narrowing (accepted maximum difference for each pair = ±7.5%; difference between ruptured and control plaques = 0.8% ± 3.1%). Plaques with the most similar IVUS reference vessel size (difference between ruptured and control plaques = 1.0 ± 3.4 mm^2) were then used to form matched pairs. The rationale of forming this control group was to identify potential differences between ruptured plaques and plaques of patients who did not have acute coronary syndromes and showed no IVUS-evident plaque rupture.

Clinical demographics. The clinical data of the study population and the matched control group were obtained independently by a physician who was not involved in the interventional protocol or the IVUS analysis. Cardiovascular risk factors that were recorded included diabetes mellitus (medication-dependent only), hypertension (medication-dependent only), hypercholesterolemia (medication-dependent or total serum cholesterol >200 mg/dl), a history of smoking and a family history of coronary artery disease.

IVUS imaging protocol. Intravascular ultrasound imaging was performed after intracoronary injections of 200 μg nitroglycerin. Intravascular ultrasound studies were performed with commercially available systems. The first IVUS system was a mechanical sector scanner (Boston Scientific Corporation, San Jose, California) incorporating a 30 MHz single-element beveled transducer rotating at 1,800 rpm. The second system was a solid-state device (Endosonics, Rancho Cordova, California). With both systems, the transducer was withdrawn using a motorized pullback device (17). Transducer pullbacks were started as distal as possible, and the entire artery was imaged to the aorto-ostial junction. In addition, the site of plaque rupture was studied with manual interrogation. Detailed IVUS criteria of plaque rupture have been reported previously (25). In brief, a plaque with an echolucent zone that communicates with the lumen and shows a fine-granular pattern of echo speckle, rapidly changing over time (similar or equal to blood inside the lumen), was considered as ulcerated ruptured plaque. The communication with the lumen was demonstrated by

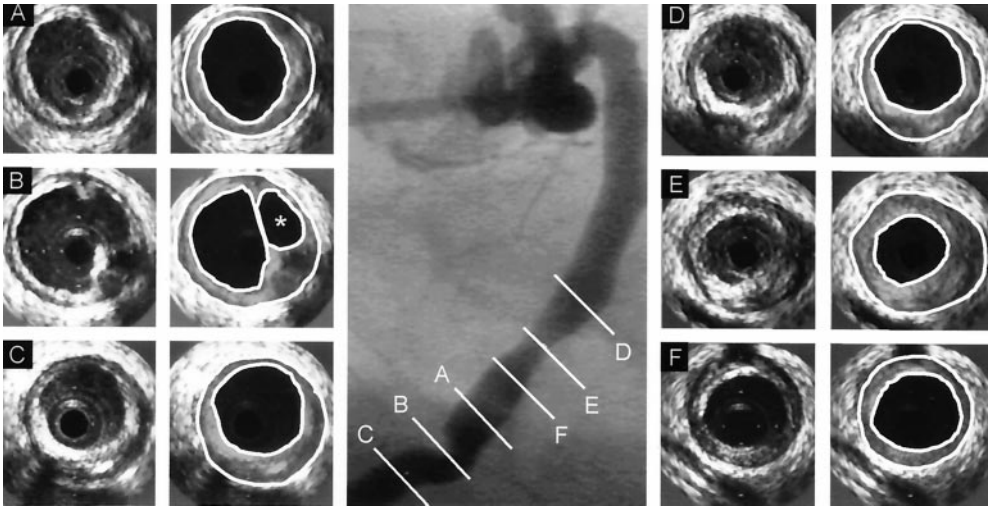

Figure 1. Example of ruptured and nonruptured plaques in right coronary artery. Intravascular ultrasound (IVUS) images of proximal reference, target site and distal reference of ruptured plaque **(A–C)** and nonruptured plaque **(D–E)** are shown on side panels. Sites of IVUS image acquisition are indicated on angiogram **(center)**. Schemes next to IVUS images indicate boundaries of lumen, external elastic membrane and cavity inside ruptured plaque **(*)**. Note eccentric plaque distribution and lumen position at site of plaque rupture **(B)**.

bolus injection of dye or saline during the IVUS investigation. Adjacent nonruptured plaques had to be separated from the ruptured plaque by an angiographically normal segment and a segment with only mild atherosclerotic changes by IVUS. All IVUS examinations were recorded on 0.5-in high-resolution super VHS tape for offline analysis.

IVUS analysis. Each case was analyzed by an experienced IVUS analyst and overread by two experienced cardiologists. The external elastic membrane (EEM) area (representing the area within the border between the hypoechoic media and the echoreflective adventitia) was measured by tracing the leading edge of the adventitia (reproducible measure of the total arterial area). As in many previous IVUS studies, plaque+media (P+M = EEM minus lumen) area was used as a measure of atherosclerotic plaque because IVUS cannot measure media thickness accurately. In our laboratory, the intraclass correlation coefficient is 0.99 for repeated measurements of EEM, 0.96 for lumen and 0.99 for P+M area.

In ruptured plaques we also measured the area of the cavity inside the plaque (plaque cavity area); this has previously been described (25) and was added to the P+M area. Accordingly, lesion P+M area of ruptured plaques represents an estimate of plaque area before plaque rupture. The lesion image slice that was analyzed had the smallest lumen area; if there were several slices with equal lumen size, the one with largest EEM and P+M area was analyzed. The arc of disease-free wall (in degrees) was measured with a lumen-centered protractor. The maximal P+M thickness (P+M-Tmax), minimal P+M thickness (P+M-Tmin), and EEM diameter at the location of P+M-Tmax (EEM-D1) were also measured (13).

To assess plaque distribution, a lumen eccentricity index was calculated by dividing (EEM-D1 + P+M-Tmax − P+M-Tmin) by (EEM-D1 − P+M-Tmax + P+M-Tmin) (13). That index gives an estimate of the shift of the center of the lumen from the center of the EEM. A value of 1 indicates that the center of the lumen coincides with the center of the EEM; a value >1 indicates that the center of the lumen is shifted from the center of the EEM.

Lesion plaque composition was assessed visually as previously described (26). If plaques predominantly consisted of tissue less dense (i.e., low echogenicity) than the reference adventitia, they were classified as soft. Plaques consisting predominantly of tissue producing echoes that were as bright as or brighter than the reference adventitia, but without acoustic shadowing, were classified as fibrous (high echogenicity), and plaques containing more than one type of tissue without evident predominance were classified as mixed.

Calcium produced bright echoes (brighter than the reference adventitia) with acoustic shadowing (attenuation) of deeper arterial structures (sometimes with reverberations). The largest total arc of target lesion calcium (in degrees) was measured using a protractor centered on the lumen. Plaques were classified as (predominantly) calcified if the largest total arc of target lesion calcium was >180°. Extrapolation of the EEM boundary behind calcium was possible, if each calcific deposit did not shadow >75° of the adventitial circumference. Thrombus formation was a heterogeneously reflecting "plaque" with layering (23), oscillating or undulating fine speckles, a rough intimal surface or a negative IVUS catheter imprint (26).

Reference segments were analyzed similar to the lesion. The proximal and distal reference segments were the most normal-looking cross-sections (smallest P+M) ≤10 mm distal and proximal to the lesion. This method of reference segment selection has been published previously (16). Reference data were the average of the proximal and distal reference.

The lesion lumen area was compared with the reference lumen area; lumen area narrowing was calculated as [1 − (lesion lumen area/reference lumen area)] × 100%. Reduction of the lesion lumen area could theoretically result from P+M increase or EEM decrease (vessel wall shrinkage). To study vascular remodeling, we compared the lesion EEM with the reference EEM to define a remodeling index: lesion/reference EEM area. Based on the value of this index, we divided the plaques into three groups: 1) values < 0.95 (shrinkage), 2) values between 0.95 and 1.05 (no remodeling) and 3) values > 1.05 (compensatory enlargement) (18).

Angiographic analysis. The AHA/ACC lesion type was assessed visually. We used the CMS system (Medis, Leiden, The Netherlands) according to standard methodology on end-diastolic frames, using the contrast-filled guiding catheter as a scaling device. The diameter function was used to determine the minimal lumen diameter and the reference diameter. The diameter stenosis was calculated as [(reference − minimal lumen diameter)/reference diameter)] × 100%.

Statistical analysis. Statistical analysis was performed by the StatView (version 5.0, SAS Institute Inc., Cary, North Carolina) and MedCalc (version 4.16, Mariakerke, Belgium) software packages for Windows. Quantitative data were given as mean ± 1 standard deviation. Qualitative data were presented as frequencies. Categorical data were compared using chi-square test or two-tailed Fischer exact test (if >20% of the cells had expected counts <5). Continuous variables were compared by analysis of variance and two-tailed (paired or unpaired) Student *t* test. To correct for multiple testing among the three groups of plaques, we first performed a three-group comparison; only if this comparison showed a significant difference were pairwise analyses performed. To compare continuous variables of the three groups of plaques, we used analysis of variance for repeated measures with post-hoc testing with the Fisher-LSD test. A value of $p < 0.05$ was considered significant.

RESULTS

Patient characteristics and angiographic data. Patients in the study population had more previous myocardial infarc-

Table 1. Clinical Characteristics of Study Population and Matched Controls

	Study Population	Matched Controls
Gender (males/females), n	26/3	26/3
Age, yrs	57 ± 11	58 ± 12
Hypercholesterolemia, n (%)	25 (86%)	20 (69%)
Hypertension, n (%)	18 (62%)	15 (52%)
Smoking, n (%)	18 (62%)	17 (59%)
Diabetes, n (%)	4 (14%)	4 (14%)
Family history of CAD, n (%)	15 (52%)	15 (52%)
Previous PTCA of another vessel, n (%)	7 (24%)	3 (10%)
Previous myocardial infarction, n (%)*	16 (55%)	4 (14%)
Angina status†		
Stable angina, n (%)	0 (0%)	25 (86%)
Unstable angina, Braunwald class I B, n (%)	3 (10%)	4 (14%)
Unstable angina, Braunwald class II B, n (%)	7 (24%)	0 (0%)
Unstable angina, Braunwald class III B, n (%)	19 (66%)	0 (0%)

Comparison was performed with chi-square test and two-tailed Fisher exact test (if > 20% of the cells had expected counts <5) as well as Student *t* test (for age only). Differences were not significant, except for previous myocardial infarction and angina status (*p = 0.003 and †0.03, respectively).

CAD = coronary artery disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

tion and presented more frequently with unstable angina than did the matched controls (Table 1). For the two groups of patients, there was no significant difference in the presence of one-, two- and three-vessel disease (31%, 38% and 31% vs. 48%, 41% and 11%, respectively). Following coronary angiography and IVUS, four (14%) patients with diffuse three-vessel disease underwent bypass surgery, 20 (69%) patients were treated by percutaneous interventions (balloon angioplasty in five [17%] and stenting in 15 [52%] patients), whereas no intervention was performed in five patients (17%). Target sites of these interventions were not necessarily identical with the ruptured or nonruptured plaques. Ruptured, nonruptured and control plaques showed no significant difference in lesion length (9.6 ± 4.1 mm, 9.1 ± 4.3 mm and 9.4 ± 4.6 mm, respectively), minimal lumen diameter (1.77 ± 0.61 mm, 1.75 ± 0.52 mm and 1.87 ± 0.44 mm), reference diameter (3.10 ± 0.63 mm, 3.19 ± 0.58 mm and 3.14 ± 0.50 mm) and diameter stenosis (43% ± 16%, 45% ± 14% and 40% ± 13%) as measured by quantitative coronary angiography. However, ruptured plaques were more frequently classified as angiographically complex lesions (Table 2, $p < 0.0001$).

Lesion location and IVUS plaque composition. Ruptured plaques were located in the left main (n = 1), left anterior descending (12), left circumflex (2) and right (14) coronary arteries. They were proximal (14), mid (11) and distal (2) in location. Some calcium was present in 15 (52%) ruptured, 17 (59%) nonruptured and 18 (62%) control plaques (NS). The total arc of calcium was 44 ± 55° ruptured, 64 ± 79° nonruptured and 79 ± 90° control (NS), respectively; predominant calcium was found in one (3%), four (14%) and four (14%) plaques (NS). Predominantly soft plaque composition (i.e., low echogenicity) was more frequently found in the ruptured and adjacent nonruptured plaques than in the control plaques ($p = 0.01$ and 0.02, Table 2). Thrombus formation was observed in eight ruptured plaques, but not in any nonruptured or control plaques.

Table 2. Qualitative Angiographic and IVUS Data

	Ruptured Plaques	Nonruptured Plaques	Control Plaques
AHA/ACC angiographic lesion type*			
Type A, n (%)	1 (4)	14 (48)	13 (45)
Type B1, n (%)	11 (38)	14 (48)	13 (45)
Type B2, n (%)	12 (41)	1 (4)	3 (10)
Type C, n (%)	5 (17)	0 (0)	0 (0)
Predominant IVUS plaque composition†			
Soft, n (%)	10 (34%)	9 (31%)	2 (7%)
Fibrous, mixed, or calcified, n (%)	19 (66%)	20 (69%)	27 (93%)

*There was a significant difference in AHA/ACC angiographic lesion type among the three groups ($p < 0.0001$, two-tailed Fisher exact test); pairwise comparison demonstrated a significant difference between ruptured vs. nonruptured and control plaques ($p < 0.0001$, both). †There was a significant difference in predominant IVUS plaque composition among the three groups ($p = 0.03$, chi-square test); pairwise comparison showed that control plaques were less often soft than both ruptured ($p = 0.01$) and nonruptured ($p = 0.02$) plaques.

AHA/ACC = American Heart Association/American College of Cardiology; IVUS = intravascular ultrasound.

Quantitative IVUS data. When ruptured plaques were compared with nonruptured plaques, there was no difference in reference EEM and lumen areas and no difference in lesion lumen area and lumen area narrowing (Table 3). However, the lesion EEM and P+M areas were larger and the position of the lumen was more eccentric. These differences were even more striking when ruptured plaques were compared with control plaques. In addition, the arc of disease-free vessel wall was larger opposite the ruptured plaques than opposite the control plaques. Both ruptured and nonruptured plaques showed a preponderance of compensatory enlargement or no remodeling and differed significantly from the control plaques ($p = 0.0001$ and 0.003, respectively). Control plaques showed increased shrinkage (Fig. 2). Ruptured and nonruptured plaques had a similar pattern of remodeling (identical remodeling in 38%).

DISCUSSION

In the present study, we used IVUS to examine both a ruptured and a nonruptured plaque in the same coronary artery of patients with unstable angina. This allowed comparison of atherosclerotic plaques exposed to the same cardiovascular risk factors, having the same genetic features. Ruptured and adjacent nonruptured plaques in patients with acute coronary syndromes showed a predominance of compensatory vascular enlargement, a large plaque burden and (frequently) a disease-free arc of vessel wall. However, EEM and P+M areas were significantly larger in the ruptured plaques. In addition, ruptured plaques showed a different

Table 3. Quantitative IVUS Parameters

	Ruptured Plaques	Nonruptured Plaques	Control Plaques	p ANOVA	p #1	p #2	p #3
Lesion							
Lumen area (mm^2)	5.5 ± 1.7	5.4 ± 1.8	6.2 ± 2.7	NS			
EEM area (mm^2)	19.7 ± 6.4	17.0 ± 4.7	15.7 ± 3.4	0.01	0.04	0.003	NS
P+M area (mm^2)	14.2 ± 5.9	11.5 ± 3.8	9.5 ± 2.6	0.0003	0.02	<0.0001	NS
Lumen eccentricity index	2.02 ± 0.49	1.70 ± 0.34	1.50 ± 0.28	<0.0001	0.002	<0.0001	0.04
Arc of disease-free vessel wall (°)	89 ± 60	62 ± 65	23 ± 55	0.0004	NS	<0.0001	0.01
Plaque cavity area (mm^2)	2.3 ± 1.1						
Reference							
EEM area (mm^2)	18.0 ± 5.1	16.1 ± 4.1	17.0 ± 3.7	NS			
Lumen area (mm^2)	9.5 ± 2.8	8.9 ± 2.9	10.4 ± 3.2	NS			
Lumen area narrowing (%)	40.0 ± 15.1	37.0 ± 16.5	40.7 ± 14.1	NS			
Remodeling index	1.09 ± 0.13	1.06 ± 0.14	0.93 ± 0.14	<0.0001	NS	<0.0001	0.0007

For each variable, ANOVA for repeated measures was performed to compare all three groups; if a significant difference was found, post-hoc Fisher-LSD test was performed for further pairwise comparison: #1 = ruptured vs. nonruptured plaques, #2 = ruptured vs. control plaques, and #3 = nonruptured vs. control plaques.
ANOVA = analysis of variance; EEM = external elastic membrane; NS = not significant; P+M = plaque plus media.

pattern of plaque distribution, with a more eccentric position of the lumen compared with the adjacent nonruptured plaques. These differences were even more striking when ruptured plaques were compared with matched control plaques.

IVUS assessment of ruptured plaques. Although a comprehensive histopathologic validation study of IVUS characteristics of ruptured plaques has not yet been reported (mainly because of difficulties in obtaining the samples required), there is ample evidence that plaque rupture can be detected by IVUS (21,22,24,25,27,28). Conversely, corresponding angiograms may or may not show luminal craters or other evidence of plaque rupture (25).

The observation of calcium being present in 52% of the ruptured plaques in this study agrees with previous IVUS studies reporting target lesion calcium in 32% to 61% of patients with unstable angina (20,23,29), and in 22% to 67% of patients with ultrasound-documented plaque rupture

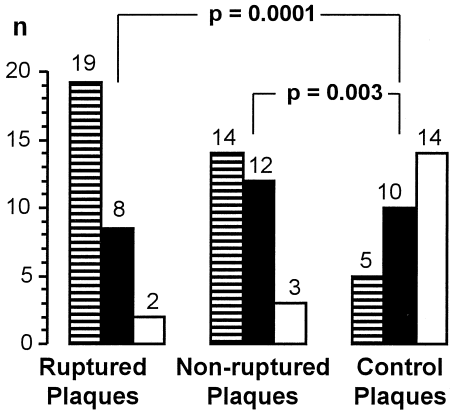

Figure 2. Vascular remodeling data. Compensatory enlargement was predominant remodeling type in ruptured and nonruptured plaques (66% and 48%), whereas shrinkage was most frequently observed in control plaques (48%). Data are absolute frequencies (n = 29 for each group). The remodeling pattern differed significantly among the three groups (p = 0.0002, Fisher exact test); pairwise comparison revealed significant differences between ruptured and nonruptured plaques vs. control plaques (p = 0.0001 and 0.003, respectively). **Striped bars:** compensatory, **Black bars:** no remodeling, **White bars:** shrinkage.

(24,25). Predominantly soft plaque, which we found in 34% of the ruptured and 31% of the nonruptured plaques in the same artery, has previously been described in 58% to 65% of patients with unstable angina (20,29). Internal shear stresses at the transition from calcium to soft plaque may be an important trigger of plaque rupture (5).

Plaque distribution. In the present study, ruptured plaques showed a significantly more eccentric position of the lumen than both nonruptured plaques in the same artery and matched controls. Our findings agree with previous histologic (1,4–6) and IVUS data (24,25), which showed eccentricity in 73% to 94% of lesions with ultrasound-documented plaque rupture. In addition, Yamagishi et al. (27) recently reported a predominance of an eccentric pattern in 12 plaques, which subsequently caused acute coronary events during a follow-up period.

The arc of disease-free vessel wall in ruptured plaques was slightly larger than in adjacent nonruptured plaques and significantly larger than in plaques of the matched controls. A disease-free portion of vessel circumference may be important for plaque rupture. Recent in vivo data demonstrated that heterogeneous vessel wall distensibility can be found at the site of non-circumferential atherosclerosis (30); this increases mechanical stress and may result in plaque disruption. These in vivo observations are supported by histopathologic data (6) showing a predominance of plaque rupture at the transition between eccentric plaques and normal vessel wall. Computer modeling indicates that stress on the fibrous cap is concentrated near its junction with the normal vessel wall (5).

Vascular remodeling. In the present study, both ruptured and nonruptured plaques in the same artery showed a predominance of compensatory remodeling. Moriuchi et al. (24) observed compensatory remodeling in 11 of 22 ruptured plaques. Smits et al. (19) observed shrinkage in four of eight patients with stable angina and compensatory enlargement in seven of 12 patients with unstable angina. Gyñgyösi et al. (20) examined patients with unstable angina and reported that compensatory enlargement was found in no

more than 37% of all plaques; however, 16 of 26 plaque ruptures were located in lesions with compensatory enlargement.

Plaque disruption may result in hemorrhage and thrombus formation, which may change plaque geometry (3) and vascular remodeling. However, the findings of the present study are supported by in vitro work of Pasterkamp et al. (31), who recently reported that histopathologic markers of plaque vulnerability were associated with compensatory enlargement in atherosclerotic vessels that had not (yet) undergone plaque rupture. In addition, Yamagishi et al. (27) recently used IVUS to demonstrate a predominantly eccentric plaque distribution of plaques, which subsequently triggered acute coronary events.

Study limitations. IVUS studies are somewhat biased because total occlusions and very tight lesions are not accessible. In addition, some ruptured plaques with very small cavities may have been missed, especially if the cavity was filled by thrombus or the flap was reattached. Not all ruptures may present a cavity. However, previous studies suggest that ruptures that are not visualized as a cavity show the same characteristics (19,20,31). Note that the terms "ruptured" and "nonruptured" refer to the situation of the plaque at the time of examination only, and that previous ruptures of plaques cannot be excluded. The matching process did not involve age; nevertheless, there was no difference in age between the study and control groups.

As in all previous IVUS studies, intracoronary injections of nitrates were used to prevent vasospasm, and no angiographic changes were observed before and after imaging; nevertheless, this does not completely exclude local vasospasm. In addition, remodeling of the reference segments may affect the assessment of lesion site remodeling. Because ostial plaques were not included in this study, our findings may not be applicable for such plaques.

Implications of the study. The approach used in the present study is unique, as it allowed comparison of ruptured and nonruptured plaques with the same genetic information, exposed to the same cardiovascular risk factors. We extracted from more than 50 patients with unstable angina and IVUS-confirmed plaque rupture a total of 29 plaques with an additional focal nonruptured plaque in an adjacent segment. Both ruptured and adjacent nonruptured plaques showed a predominance of compensatory vascular enlargement, a large plaque burden and frequently a disease-free arc of vessel wall. But ruptured plaques showed a different pattern of plaque distribution, with a significantly more eccentric position of the lumen. This difference was even more striking when ruptured plaques were compared with matched control plaques derived from our database without evidence of plaque rupture or acute coronary syndromes. The findings of this study suggest that intravascular ultrasound assessment of plaque distribution and vascular remodeling may help to identify plaques with the highest probability of spontaneous rupture. This may be useful for the evaluation of therapeutic approaches such as aggressive lipid lowering or local drug delivery.

Reprint requests and correspondence: Dr. Clemens von Birgelen, Department of Cardiology, University Hospital Essen, Hufelandstr.55, D-45122 Essen, Germany. E-mail: von.birgelen@uni-essen.de.

REFERENCES

1. Davies M, Thomas A. Thrombosis and acute coronary artery lesions in sudden cardiac ischemic death. N Engl J Med 1984;310:1137–40.
2. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med 1992;326:242–50, 310–18.
3. Theroux P, Fuster V. Acute coronary syndromes: unstable angina and non-Q-wave myocardial infarction. Circulation 1998;97:1195–206.
4. Falk E. Plaque rupture with severe pre-existing stenosis precipitating coronary thrombosis: characteristics of coronary atherosclerotic plaques underlying fatal occlusive thrombi. Br Heart J 1983;50:127–34.
5. Richardson PD, Davies MJ, Born GVR. Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques. Lancet 1989;2:941–4.
6. Qiao JH, Fishbein MC. The severity of coronary atherosclerosis at site of plaque rupture with occlusive thrombosis. J Am Coll Cardiol 1991;17:1138–42.
7. Little WC, Constantinescu M, Applegate RJ, et al. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? Circulation 1988;78:1157–66.
8. Fishbein MC, Siegel RJ. How big are coronary atherosclerotic plaques that rupture? Circulation 1996;94:2662–6.
9. Mann JM, Davies MJ. Assessment of the severity of coronary artery disease at postmortem examination. Are the measurements clinically valid? Br Heart J 1995;74:528–30.
10. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371–5.
11. Ge J, Erbel R, Zamorano J, et al. Coronary arterial remodeling in atherosclerotic disease: an intravascular ultrasound study in vivo. Coron Artery Dis 1993;4:981–6.
12. von Birgelen C, Airiian SG, Mintz GS, et al. Variations of remodeling in response to left main atherosclerosis assessed with intravascular ultrasound in vivo. Am J Cardiol 1997;80:1408–13.
13. Clarijs JAGM, Pasterkamp G, Schoneveld AH, van Leeuwen TG, Hillen B, Borst C. Compensatory enlargement in coronary and femoral arteries is related to neither the extent of plaque-free vessel wall nor lesion eccentricity: a postmortem study. Arterioscler Thromb Vasc Biol 1997;17:2617–21.
14. Pasterkamp G, Wensing PJW, Post MJ, Hillen B, Mali WPTM, Borst C. Paradoxical arterial wall shrinkage may contribute to luminal narrowing of human atherosclerotic femoral arteries. Circulation 1995;91:1444–9.
15. Nishioka T, Luo H, Eigler NL, Berglund H, Kim CJ, Siegel RJ. Contribution of inadequate compensatory enlargement to development of human coronary artery stenosis: an in vivo intravascular ultrasound study. J Am Coll Cardiol 1996;27:1571–6.
16. Mintz GS, Kent KM, Pichard AD, Satler LF, Popma JJ, Leon MB. Contribution of inadequate arterial remodeling to the development of focal coronary artery stenoses: an intravascular ultrasound study. Circulation 1997;95:1791–8.
17. von Birgelen C, Mintz GS, de Vrey EA, et al. Atherosclerotic coronary lesions with inadequate compensatory enlargement have smaller plaque and vessel volumes: observations with three-dimensional intravascular ultrasound in vivo. Heart 1998;79:137–43.
18. Smits PC, Bos L, van Ufford MAQ, Eefting FD, Pasterkamp G, Borst C. Shrinkage of human coronary arteries is an important determinant of de novo atherosclerotic luminal stenosis: an in vivo intravascular ultrasound. Heart 1998;79:143–7.
19. Smits PC, Pasterkamp G, de Jaegere PPT, de Feyter PJ, Borst C.

Angioscopic complex lesions are predominantly compensatory enlarged: an angioscopic and intracoronary ultrasound study. Cardiovasc Res 1999;41:458–64.
20. Gyöngyösi M, Yang P, Hassan A, et al. Arterial remodelling of native human coronary arteries in patients with unstable angina pectoris: a prospective intravascular ultrasound study. Heart 1999;82:68–74.
21. Zamorano J, Erbel R, Ge J, et al. Spontaneous plaque rupture visualized by intravascular ultrasound. Eur Heart J 1994;15:131–3.
22. Baumgart D, Liu F, Haude M, Görge G, Ge J, Erbel R. Acute plaque rupture and myocardial stunning in patient with normal coronary arteriography. Lancet 1995;346:193–4.
23. Kearney P, Erbel R, Rupprecht HJ, et al. Differences in the morphology of unstable and stable coronary lesions and their impact on the mechanisms of angioplasty: an in vivo study with intravascular ultrasound. Eur Heart J 1996;17:721–30.
24. Moriushi M, Saito S, Takaiwa Y, et al. Assessment of plaque rupture by intravascular ultrasound. Heart Vessels 1997;12 Suppl:178–81.
25. Ge J, Chirillo F, Schwedtmann J, et al. Screening of ruptured plaques in patients with coronary artery disease by intravascular ultrasound. Heart 1999;81:621–7.
26. Di Mario C, Görge G, Peters R, et al. Clinical application and image interpretation in intracoronary ultrasound. Eur Heart J 1998;19:207–29.
27. Yamagishi M, Terashima M, Awano K, et al. Morphology of vulnerable coronary plaque: insights from follow-up of patients examined by intravascular ultrasound before an acute coronary syndrome. J Am Coll Cardiol 2000;35:106–11.
28. von Birgelen C, Klinkhart W, Mintz GS, et al. Size of emptied plaque cavity following spontaneous rupture is related to coronary dimensions, not to degree of lumen narrowing. A study with intravascular ultrasound in vivo. Heart 2000;84:483–8.
29. Rasheed Q, Nair R, Hodgson JMcB. Correlation of intracoronary ultrasound plaque characteristics in atherosclerotic coronary artery disease patients with clinical variables. Am J Cardiol 1994;73:753–8.
30. Yamagishi M, Umeno T, Hongo Y, et al. Intravascular ultrasonic evidence for importance of plaque distribution (eccentric vs. circumferential) in determining distensibility of the left anterior descending artery. Am J Cardiol 1997;79:1596–600.
31. Pasterkamp G, Schoneveld AH, van der Wal AC, et al. Relation of arterial geometry to luminal narrowing and histologic markers for plaque vulnerability: the remodeling paradox. J Am Coll Cardiol 1998:32:655–62.